Europäisches Patentamt

European Patent Office

11 Publication number:

0 330 353

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(a) Application number: 89301337.5 (b) Int. Cl.4 C07D 401/06 A61K 31/445 , amains agent several ed no sache estables. Second A61K 31/41 82 //(C07D401/06,

② Date of filling: 13.02.89 great of historical violations of the metric 257:00,211:00) is a conclusioner viseases, and group conticular visids act as post septiments as accordingly in School of

Suropean Power Rublication 025/2891 From a cast of phosphoric act populative derivatives which

Claims for the following Contracting States: ES + GR

- Priority: 19.02.88 US 157760
- 43 Date of publication of application: 30.08.89 Bulletin 89/35
- Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE
- Applicant: ELI LILLY AND COMPANY **Lilly Corporate Center** Indianapolis Indiana 46285(US)
- Inventor: Ornstein, Paul Leslie 1850 Electric Avenue Indianapolis Indiana 46260(US)
- Paper Representative: Tapping, Kenneth George et $\mathsf{al}_m \mathbb{Y}$ Eri Wood Manor Windlesham Surrey, GU20 6PH(GB)
- Tetrazole excitatory amino acid receptor antagonists.
- The present invention provides novel tetrazole derivatives useful as excitatory amino acid receptor antagonists and in treating a variety of associated nervous system disorders.

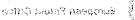
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TETRAZOLE EXCITATORY AMINO ACID RECEPTOR ANTAGONISTS

The present invention relates to novel tetrazole derivatives which are antagonists of excitatory amino edecedent in the base of the companies

As the science of medicine continues to advance, a need is seen for more specific and mechanistically determinate pharmaceutical agents. It is no longer acceptable to treat the patient's symptoms only; the goal of modern medicine is to identify the underlying mechanism of disease and to treat that. Accordingly, there is a demand for pharmaceuticals which have specific, predictable effects on the body's mechanisms. The mechanisms of the central nervous system are particularly important in many dangerous and distressing diseases, and pharmaceuticals which act on those mechanisms are accordingly in demand.

European Patent Publication 0203891 shows a class of phosphonic acid piperidine derivatives which antagonize the excitatory amino acid receptor. Those compounds, however, are undesirably reactive:

The present invention provides compounds of the formula

BD 4 15 DETYER BUILDS, SOLET LYMONY (P) native to particultion of application 38,06.65 Ruleith 39/36 (P) Designated Contracting Styles. AT BE ON DE ES FR GE CH IN LL LU HE EE 福油油物油锅料品 R1 Tetrace element was also come yesteres element (9) egostric languages and Granda (Language Harrison) and stay of Crastation independent moderners increased with 🗑

wherein:

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$$R^{1}$$
 is $-COR^{3}$, $-CN(R^{4})_{2}$, $-CNHSR^{3}$, $-CNHCR^{3}$ or $N - N - R^{2}$

and in teaching a vient in the special and the control of the stain

R2 is hydrogen or C1-C3 alkyl;

n is 0, 1, 2 or 3;

m is 0 or 1;

provided that the sum of m and n is 0, 1, 2 or 3;

R3 is hydrogen, C1-C4 alkyl, phenyl or an oral ester forming group;

Y is -CH=;

each R4 independently is hydrogen, C1-C4 alkyl or phenyl; or

a pharmaceutically acceptable salt thereof.

The invention also provides pharmaceutical formulations comprising a compound of Formula I and a pharmaceutically acceptable carrier, diluent or excipient therefor.

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The invention also provides a process for preparing a compound of the formula

with an artiful of the formula HNHSO/32 or HNHOOPS. C) altylating a compound of the formula.

comprising:

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A) esterifying a compound of the formula

How a naticle of the formula ARP wherein RF is Gr-Da alloy and X is promo, chloro or lodo;

Di deblocking a compound of the formula

with an alcohol of the formula HOR3, wherein R3 is C1-C4 alkyl, phenyl or an oral ester forming group;

B) aminating a compound of the formula

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The invention are provided a process for preparing a compount or the formula

with an amine of the formula $HN(R^4)_2$, $HNHSO_2R^3$ or $HNHCOR^3$; C) alkylating a compound of the formula

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comprising: 4) extentying a compound of the formula

ΙV

with a halide of the formula X-R² wherein R² is C₁-C₃ alkyl and X is bromo, chloro or iodo;

D) deblocking a compound of the formula

with an alcohol of the formula MOR), wherein RY (\$13)-13, about othernyt or an oral eater forming group;

(5) similaring a compound of the formula \$9.0 - \cdots \c

by acidic or basic hydrolysis; or

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E) preparing a salt of a compound of formula I with an acidic or basic salt-forming reagent.

Further embodiments of the invention include a method of blocking one or more excitatory amino acid receptors, as well as methods for treating a variety of disorders which have been linked to the excitatory amino acid receptors including neurological disorders (for example, epilepsy), stroke, anxiety, cerebral ischaemia, muscular spasms and neurodegenerative disorders such as Alzheimer's Disease and Huntington's Disease, employing a compound of Formula I.

In the above formula, the terms "C₁-C₃ alkyl" and "C₁-C₄ alkyl" represent a straight or branched alkyl chain having from one to four carbon atoms, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and t-butyl.

The term "oral ester forming group," as used herein, represents a substituent which, when attached to the carboxylic acid group, forms an ester function suitable for administration to mammals in need of substituted on the carboxylic benzylic benz

While all the compounds of the present invention are believed to be antagonists of excitatory amino acid receptors, there are certain compounds of the invention which are preferred for such uses Preferably, and the compounds of the invention which are preferred for such uses Preferably, and the compounds of the invention which are preferred for such uses Preferably, and the compounds of the invention which are preferred for such uses Preferably.

*xox On the description of the preferred aspects of the present invention will be noted berinafter than a special property of the present invention will be noted berinafter than a special property of the present invention will be noted berinafter than a special property of the present invention will be noted bereinafter than a special property of the present invention will be noted bereinafter than a special property of the present invention will be noted bereinafter than a special property of the present invention will be noted bereinafter than a special property of the present invention will be noted bereinafter than a special property of the present invention.

The compounds of the present invention possess two asymmetric carbon atoms represented by the carbon atom of the piperidine ring which attaches to the tetrazole ring either directly or through one or more methylene groups, and the carbon atom of the piperidine ring which attaches R1 to the piperidine ring. As such, the compounds can exist as two diastereoisomers, their cis or trans isomers, and each of which can exist as the racemic mixture of such isomers or each individual optical isomer. Accordingly, the compounds of the present invention will include not only the (±)-racemates, but also their respective optically active (+)-and (-)-isomers. When a Y group is present, it creates a third point of asymmetry, and the compounds accordingly include the E and Z isomers and the corresponding racemate.

As pointed out above, this invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. These salts can exist in conjunction with the acidic or basic portion of the molecule and can exist as acid addition, primary, secondary, tertiary or quaternary ammonium or alkali metal or alkali earth metal salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydrolodic, sulfuric and phosphoric acid, as well as organic acids such as paratoluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, ammonium, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, lithium, bromide, iodide, acetate, magnesium, propionate, tetramethylammonium, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, potassium, propiolate, oxalate, trimethylammonium, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, sodium, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, methylammonium, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, calcium, β-hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts.

Compounds of the present invention will contain one or two tetrazole rings. Tetrazole is known to exist as tautomeric structures. The tetrazole having the double bond on the nitrogen atom at the 1-position and the R² substituent on the N-2 nitrogen atom is properly named as a 2H-tetrazole and is represented by the following structure:

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This compound has a corresponding tautomeric form wherein the R2 substituent is at N-1 with the double bond on the nitrogen atom of the 4-position. These compounds are named in part as 1H-tetrazoles and possess the following part structure:

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In the part of the meaning of the property and the part and Mixtures of the two tautomers are referred to herein as 1(2)H-tetrazoles. The present invention contemplates and you talk the state of the two talks and the combination of the two talks are the combination of the combination of

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The compounds of the present invention may be prepared by procedures well known to those of ordinary skill in the art. Preferably, a hydroxy or hydroxyalkyl substituted 2-carbalkoxypyridine is reduced to the corresponding hydroxy or hydroxyalkyl substituted 2-carbalkoxypiperidine, which is blocked at the ring nitrogen with a standard blocking reagent. The blocked hydroxy or hydroxyalkyl substituted:2-carbalkoxypiperidine is converted to the halo or haloalkyl substituted 2-carbalkoxypiperidine, which is then converted 20 to the corresponding cyano intermediate. When nois not zero, the blocked hydroxy substituted 2carbalkoxypyridine is oxidized to the ketone, which is then converted to an α, β-unsaturated nitrile, and then attento the desired cyano intermediate by hydrogenation. The cyano intermediate is converted to the blocked tetrazole: substituted 2-carbalkoxypiperidine which is hydrolyzed to the compound of the present invention.

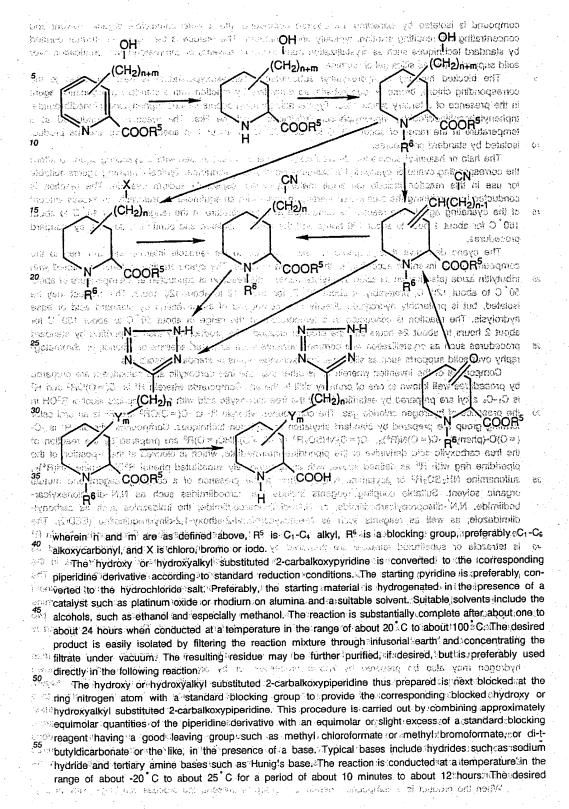
sA . This synthesis may be represented by the following scheme: a more modes, and this economic enclyment auch, the compounds can exist as two diades water are their than to be be incorrers, and each of which can oxist as the recently matury of such isomers or such just dual option isomer. Accordingly, the compounds of the present invention will moture not only fire (or mountain, but size that respective appeally notive (+)and (-)-increase. When a Y group is present if the ball of point of asymmotry, and the compounds secondinally include the E and A bounsale and the Lour inscreting recemeta.

As pointed out above, this view took receives the mean emporally acceptable sells of the compounds. defined by Foresia I. These issue one evice in the restricted acidic or basic particles of the molecula take our cold as soit adollion, principle, accorded to the contract are managed to a alkali transit or alkali aetor meta stital Adda componir schouget. I figur un in deta briede in meta acide stob as hydrochlo--anagrikas disarri koloni igi ogas jasi hakri jenki jo ori kiko saha, naki oli Asse sahbuhahyih pamardadoyih pen 35.s plesonal principal calculate granularia contributo e espera i nel per propria productiva parabatementatio acusto seed, and repaised indeplate with frighten of the representational action and strike strike that stati odov sob prekui – prekar se star. Selection of the design of the selection न्द्रमधून्यत् । अस्त्रीनपूर्वे । अनुसर्वे । अन्य अभिन्यः । अस्त्रीयम् । अस्त्रीयम् । अस्त्रीयम् । The state of the second The control of the factor of the control of अधिकार १ वर्षा के प्रकार करेंगा है। इस महिल्ला है 40 per and children to see at the second of the The fighteen that the same property of property. element in the partie of the property and the second section of the second second second in the mean and the engineering of the second action to the contract of especially the second ्राहरू वर्षेत्र । इति हा क्रमान्य विकास समिति

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compound is isolated by extracting the desired compound into a water-immiscible organic solvent and concentrating the resulting solution, typically under vacuum. The residue is then generally further purified by standard techniques such as crystallization from common solvents or chromatographic purification over solid supports such as silica gel or alumina.

The blocked hydroxy or hydroxyalkyl substituted 2-carbalkoxypiperidine is next converted to the corresponding chloro, bromo or iodo substituted derivative by reaction with a standard halogenating agent in the presence of a tertiary amine base. Typical halogenating agents include triphenylphosphinedibromide, triphenylphosphinedichloride and the like. The reaction is conducted at a temperature in the range of about -10 °C to about 25 °C for about 1 to about 12 hours and the product isolated by standard procedures.

The halo or haloalkyl substituted 2-carbalkoxypiperidine is next treated with a cyanating agent to afford the corresponding cyano or cyanoalkyl substituted 2-carbalkoxypiperidine. Typical cyanating agents suitable for use in this reaction include the alkali metal cyanides, especially sodium cyanide. The reaction is conducted by combining the brominated starting material with an equimolar to preferably an excess amount of the cyanating agent. The reaction is conducted at a temperature in the range of about 40 °C to about 150 °C for about 1 hour to about 120 hours and the product isolated and purified, if desired, by standard procedures.

The cyano derivative thus prepared is next converted to the tetrazole intermediate and then to the compound of the invention according to the following process. The cyano starting material is reacted with tributyltin azide (also known as azido tributylstannane). This reaction is conducted at a temperature of about 50°C to about 120°C, preferably at about 80°C, for about 120 hours. The product may be isolated, but is preferably hydrolyzed directly to a compound of the invention by standard acid or base hydrolysis. The reaction is conducted at a temperature in the range of about 50°C to about 150°C for about 2 hours to about 24 hours and the product isolated. The product may then be purified by standard procedures such as crystallization with common solvents such as water, acetone or ethanol, or chromatogeraphy over solid supports such as silicaget, ion exchange resins or standard absorbents.

Compounds of the invention wherein R1 is other than the free carboxylic acid substituent are prepared by procedures well known to one of ordinary skill in the art. Compounds wherein R1 is -C(=O)OR3 and R3 is C1-C4 alkyl are prepared by esterification of the free carboxylic acid with an appropriate alcohol R3OH in the presence of hydrogen chloride gas. The compounds wherein R1 is -C(=O)OR3 and R3 is an oral ester forming group are prepared by standard alkylation or acylation techniques. Compounds wherein R1 is -C-(= O)O-(phenyl), $-C(= O)N(R^4)_2$, $-C(= O)NHSO_2R^3$ or $-C(= O)NHC(= O)R^3$ are prepared by the reaction of the free carboxylic acid derivative of the piperidine intermediate, which is blocked at the 1-position of the piperidine ring with R6 as defined above, with an appropriately substituted phenol R3OH amine NH(R4)2, sulfonamine NH2SO2R3 or acylamine NH2C(=O)R3 in the presence of a coupling reagent and mutual organic solvent. Suitable coupling reagents include the carbodiimides such as N,N'-dicyclohexylcarbodiimide, N,N diisopropylcarbodiimide, or N,N diethylcarbodiimide; the imidazoles such as carbonyldiimidazole; as well as reagents such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ). The so stresulting compound is then deblocked at the 1-position as hereinbefore described. Compounds wherein R1 is tetrazole or substituted tetrazole are prepared by hydrolyzing the cyang intermediate prepared as entitled above to the corresponding 2-carboxy derivative which is then treated with ammonia in the -not presence of a coupling reagent as described above to provide the corresponding primary carboxamide. The a to carboxamided is dehydrated ato athe acorresponding acarbonitrile auponastreatment with phenylphosphinoyl edi edichloride or triphenylphosphine dibromide, both in the presence of a tertiary, amine such as triethylamine 4558 or apyridine. The resulting acompound is converted ato the adject razole intermediate, with at least two be idequivalents of tributyltin azide according to conditions hereinbefore described. The desired compound is anti athen prepared as hereinbefore described. I was a matter of managar yit bestalogi yitase si toutboro

Compounds of the present invention wherein the R2 substituent on the tetrazole ring is other than hydrogen may also be prepared by known processes, or by processes analogous to such known processes. Typically, alkylation of the unsubstituted starting material, with an appropriate halide reagent to provides the desired compound of the invention or an intermediate, which can be further modified to a descompound of the invention as herein described. If a base is employed in the alkylation reaction, addition may also be blocked prior to the reaction, and deblocked subsequently according to standard conditions employing standard blocking reagents. Of course, disubstitution with the same substituent merely requires and in the use of an appropriate molar excess of reagent to account for each of the desired substituents on the botts final compound.

When the product is a compound wherein a Y group is present, the process can begin with an oxy-

substituted 2-carbalkoxy blocked piperidine, which is cyanated with diethyl cyanoalkylphosphonate or cyanoalkyltriphenylphosphonium halide, to prepare the desired cyanoalkylidene intermediate. The cyanogroup of it may be converted to the tetrazole, as described above, leaving the alkylidene linkage intact. Alternatively, the general process may be used by omitting the usual reduction of the cyanoalkylidene intermediate.

The preceding description of the synthesis of the compounds of the present invention prepares a mixture of the cis- and trans-isomers, but predominantly as the cis-isomer. The diastereomers are easily separated from the mixture using standard chromatographic techniques, for example, employing silica gel or alumina adsorbents. An isolated diastereomer may be converted to the other diastereomer by treatment with a base such as a tertiary amine base or an alkali metal alkoxide in the corresponding alcohol. While separation or conversion may be conducted on any piperidine derivative in the foregoing synthetic scheme, preferably such separation or conversion is carried out on the blocked hydroxy or hydroxyalkyl substituted 2-carbalkoxypiperidine as defined above.

The pharmacoutically acceptable salts of the Invention are typically formed by reacting a piperidinetetrazole of the invention with an equimolar or excess amount of salt forming reagent. The reactants are generally combined in a mutual solvent such as diethyl ether, benzene, ethanol or water and the salt normally precipitates out of solution within about one hour to 10 days, and can be isolated by filtration.

The hydroxy or hydroxyalkyl substituted 2-carbalkoxypyridines employed as starting materials in the synthesis of the compounds of this invention are known and easily prepared by procedures well known to those of ordinary skill in the art. For example, a pyridyl(C1-C4)alkanoic acid ester-is converted to the corresponding hydroxy substituted pyridine, which is acylated and converted to the N-oxide derivative. The acylated(N-oxide)pyridine is converted to a 2-cyano(acylated)pyridine which is finally converted to a hydroxy or hydroxyalkyl substituted 2-carbalkoxypyridine. This reaction may be represented by the self-of-lowing scheme:

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aged. The reculting mixing was salped at compared and

has wherein n and m are as defined above, R5 is C1-C4 alkyl and R7 is hydrogen or methyl.gar a graph and

The following Examples further illustrate the compounds of the present invention and methods for their synthesis. The Examples are not intended to be limiting to the scope of the invention in any prespect and see should not be so construed.

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The control of the state of the

cis-(±)-4-[2-(1(2)H-Tetrazol-5-yl)ethyl]-2-piperidinecarboxylic acid

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Fifteen grams (0.091 mol) of 4-pyridineacetic acid ethyl ester was dissolved in 180 ml of dry THF. The solution was transferred to a 1 L. 3-neck round bottom flask which had been flushed with nitrogen. To the mixture was added dropwise 55 ml of 1.0 M lithium aluminum hydride (0.055 mol) at approximately 0 °C. The reaction mixture became yellow upon addition of the reducing agent. Following addition, the mixture was quenched with 2.1 ml of water at 0 °C followed by 2.1 ml of 15% by volume of sodium hydroxide and 15 6.3 ml of water. The mixture was allowed to stir at room temperature for approximately 4 hours and filtered through Celite. The filtrate was concentrated under vacuum to provide 6.38 g of 4-pyridineethanol. This material was used directly in the following reaction.

synthesis of the autograph of this formal professional section of the section of 20 B. 4-Pyridineethanol acetate seconds and the second the second to each the second the second to be each to be second to

o do elektron kodi enirgi izeren dir. Del in diene er britik lenilakon fribilitzki e virinleri enibriogeenda To a solution of 11.3 ml of acetic anhydride in 100 ml of methylene chloride was added approximately 125 mg of dimethylaminopyridine, and the solution was cooled to 0 C. In a separate container 12.2 g (0.099 mol) of 4-pyridineethanol was suspended in 80 ml of methylene chloride and 12.14 g (0.120 mol, 16.7 ml) of triethylamine was added. This mixture was added to the acetic anhydride solution slowly by pipet. The resulting mixture was stirred at room temperature for approximately 90 minutes and quenched with about 100 ml of water. The mixture was placed in a separatory funnel and the organic layer was isolated and washed two times with 100 ml portions of water. The aqueous layers were combined and extracted two times with methylene chloride and one time with diethyl ether. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to provide 16.2 g of the desired compound. Purification by high pressure liquid chromatography provided 11:19 g of 4pyridineethanol acetate.

C. 4-Pyridineethanol acetate 1-oxide

To a solution of 38.82 g (0.18 mol, 80% by weight) of 3-chloroperoxybenzoic acid in 360 ml of acetone was added 24.70 g (0.15 mol) of 4-pyridineethanol acetate neat via pipet (20 ml acetone rinse). The reaction mixture was allowed to stir for approximately one hour at room temperature until all of the starting material had been consumed as indicated by thin layer chromatography in ethanol:ethyl acetate (1:9, v:v). The reaction mixture was concentrated under vacuum and the residue was partitioned between 300 ml of water and 300 ml of diethyl ether. The aqueous layer was separated, extracted three times with diethyl ether and the organic extracts were combined. The combined organic phases were washed three times with water. The organic layers were discarded and the combined aqueous layers were concentrated under vacuum. The resulting residue was dissolved in chloroform and the solution was dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was dried under vacuum to afford 24.06 g of 4pyridineethanol acetate 1-oxide which was used directly in the following reaction.

D. 4-[2-(Acetyloxy)ethyl]-2-pyridinecarbonitrile

To a solution of 24.06 g (0.13 mol) of 4-pyridineethanol acetate 1-oxide dissolved in 260 ml of methylene chloride was added 15.87 g (0.16 mol, 21.4 ml) of trimethylsilylcyanide. The mixture was stirred for approximately 5 minutes and 17.21 g (0.16 mol, 16.6 ml) of N,N-dimethylcarbamoyl chloride was added. The reaction was mildly exothermic. The mixture was stirred at room temperature overnight and 440 ml of 10% by weight aqueous potassium carbonate was added carefully. The mixture was stirred for approximately 15 minutes and the organic layer was separated. The aqueous layer was extracted three times with methylene chloride and the organic extracts were combined, dried over anhydrous sodium sulfate and

concentrated under vacuum to afford 25.5 g of the desired compound. This material was chromatographed to provide 18.45 g of 4-[2-(acetyloxy)ethyl]-2-pyridinecarbonitrile as rebrear off-white solid mp* = 49*-52*C. The desired compound is missed in the control of the control of

iville E. Methyl 4-(2-hydroxyethyl)-2-pyridinecarboxylate े किल न प्रशास हुन्हीयल को अधीकारी हिन्नी होती होती कार्या

A 1 I. round bottom flask was charged with 18.24 g (0.096 mol) of 4-[2-(acetyloxy)ethyl]-2-pyridinecarbonitrile and 380 ml of methanol. To the reaction mixture was added 96 ml of 5N aqueous potassium

The residue was again auginetic in thus so no seem some said the Ab are continued with

hydroxide and the reaction mixture was refluxed overnight with stirring. The reaction mixture was cooled and concentrated under vacuum. To the residue was added methanol saturated with hydrochloric acid (400 ml), and the resulting mixture was heated to reflux for 30 minutes, cooled and concentrated under vacuum. To the residue was added 400 ml of methanol saturated with hydrochloric acid. The mixture was refluxed overnight, cooled to room temperature and concentrated under vacuum. The mixture was partitioned between methylene chloride and 20% by weight potassium bicarbonate in water. The was partitioned between methylene chloride and 20% by weight potassium bicarbonate in water. The was partitioned in diethyl ether. The organic extracts were combined, dried over anhydrous sodium sulfate; filtered and concentrated under vacuum to provide 11.51 g of the desired compound. The vaqueous layer was concentrated to approximately half its original volume, extracted three times with methylene chloride and one time with diethyl ether. The organic extracts were combined, dried over anhydrous sodium sulfate and concentrated under vacuum as described above to provide an additional 1:15 g of the desired compound.

The crude products were combined and purified by high pressure fliquid chromatography to provide 9.02 g -1-M-for methyl 4-(2-hydroxyethyl)-2-pyridinecarboxylate as a clear oil and the combined batton in 0.03 A .L. two entities a set of the combined purification of the combined

bits (F.) Methylicis-4-(2-hydroxyethyl)-2-piperidinecarboxylate box observed into between boseliom to the lydratic to the 0.00 page analysisching bits in in 0.00 pages analysisching bits in in 0.00 pages analysisching bits in in 0.00 pages analysisching bits in inc.

Methyl 4-(2-hydroxyethyl)-2-pyridinecarboxylate (9.02 g, 0.050 mol) was placed in a 250 ml round bottom flask and 100 ml of methanol saturated with gaseous hydrochloric acid was added (pH 1). The resulting solution was concentrated under vacuum to afford 10.98 g of the hydrochloride salt. This material was hydrogenated at 50 °C and 60 p.s.l. overnight employing 89 ml of methanol and 1/8 g of platinum boxide. The mixture was filtered through Cellte, washed with methanol and concentrated under vacuum to provide 10.64 g of methyl cis-4-(2-hydroxyethyl)-2-piperidinecarboxylate, used directly without purification.

© 393- 005. The carbondin one of professional equal S-fly rise(ty-3-logardel-big. Methyl cis-4-(2-hydroxyethyl)-N-t-butoxycarbonyl-2-piperidinecarboxylate

To a 500 ml round bottom flask was added 10.64 g (0.048 mol) of methyl cis-4-(2-hydroxyethyl)-2-piperidinecarboxylate and 160 ml of methylene chloride. To the mixture was added 18.10 g (0.14 mol, 24.4 ml) of Hunig's base and the resulting mixture was gently agitated until all the starting material was dissolved. The mixture was cooled to 0°C, 12.66 g (0.058 mol, 13.3 ml) of di-t-butyldicarbonate was added and the mixture was stirred overnight warming to room temperature. To the mixture was added 200 ml of methylene chloride, and the solution was washed three times with 100 ml portions of an aqueous solution of 10% by weight sodium bisulfate. The aqueous layers were combined and extracted twice with methylene chloride and once with diethyl ether. The organic extracts were combined and extracted twice with methylene chloride and once with diethyl ether. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to provide 16.31 g of residue. High pressure liquid chromatography of the residue provided 11.58 g of methyl cis-4-(2-hydroxyethyl)-N-t-butoxycarbonyl-2-piperidinecarboxylate.

H. Methyl cis-4-(2-bromoethyl)-N-t-butoxycarbonyl-2-piperidinecarboxylate

Dibromotriphenylphosphine was prepared by combining 9.00 g (0.035 mol) of triphenylphosphine and 5.50 g (1.80 ml, 0.035 mol) of bromine in 90 ml of methylene chloride at 0 °C. To this mixture was added 9.00 g (0.031 mol) of methyl cis-4-(2-hydroxyethyl)-N-t-butoxycarbonyl-2-piperidinedicarboxylate and 3.70 g (3.8 ml, 0.047 mol) of pyridine in 10 ml of methylene chloride. The reaction mixture was stirred for one hour

at 0 C and diethyl ether was added. The reaction mixture was washed twice with an aqueous solution of 10% by weight sodium bisulfate, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting residue was suspended in diethyl ether, filtered and concentrated under vacuum. The residue was again suspended in diethyl ether and filtered, and the filtrate combined with the residue from the first filtration. The resulting mixture was concentrated under vacuum to provide 12.95 g of methyl cis-4-(2-bromoethyl)-N-t-butoxycarbonyl-2-piperidinecarboxylate as an oily solid, used without further pure reficcation in the mexture action.

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To a solution of 12.95 g (0.031 mol, containing triphenylphosphine oxide) of methyl cis-4-(2-bromoethyl)-N-t-butoxycarbonyl-2-piperidinecarboxylate and 40 ml of DMSO was added 2.30 g (0.047 mol) of sodium cyanide. The mixture was stirred for approximately 30 minutes at 50 °C, To the mixture was added 50 ml each of water and brine and the mixture was extracted four times with methylene chloride and once with diethyl ether. The organic extracts were combined washed twice with water and once with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The resultant residue was dissolved in 100 ml of ethyl acetate hexane (1:3, v.v.) and filtered through a one inch pad of silica gel (230-400 mesh) in a 150 ml medium porosity sintered glass funnel. The silica gel pad was washed with an additional 400 ml concentrated under vacuum to afford 7.85 g of methyl cis-

J. A 250 ml round bottom flask was charged with 7.57.g (0.026 mol) of methyl cis.4-(2-cyanosthyl)-N-t-butoxycarbonyl-2-piperidinecarboxylate and 17.0 g (0.051 mol) of tributyltin azide. The resulting mixture was heated at 80° C for approximately 48 hours and cooled to room temperature. To the mixture was added 100 ml of methanol saturated with hydrochloric acid. The mixture was stirred two hours at room temperature and concentrated under vacuum. To the mixture was added 50 ml of 6N hydrochloric acid and 150 ml of diethyl other. The aqueous layer was separated and extracted again with 150 ml of diethyl other. The aqueous layer was separated and extracted again with 150 ml of 6N hydrochloric acid. The layer was concentrated under vacuum. The residue was dissolved in water, treated with 4.2 g of propylene oxide at 50° C for one hour, and concentrated under vacuum. The residue was dissolved in water, treated with 4.2 g of propylene oxide at 50° C for one hour, and concentrated under vacuum. The residue was dissolved in a minimum amount of water, and the resulting mixture was cooled to minimum. The residue was dissolved in a minimum amount of water, and the resulting mixture was cooled to minimum. The precipitated crystals were collected by vacuum filtration and washed with water, acetone and diethyl ether. The crystals were recrystallized from water to provide 3.25 g of cis-(±)-4-[2-(1(2)-H-tetrazol-5-yl)ethyl]-2-piperidinecarboxylic acid dihydrate. mp = 260°-265° C

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Analysis calculated for C₃H₁₅N₅O₂ ²2H₂O

Theory: C, 41.37; H, 7.33; N, 26.80; Theory: C, 41.60; H, 7.27; HN, 26.75; The second of the control of

The compound of Example 2 was prepared according to the general procedure described in Example 1.

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- 'V^{rigo}cis-(±)-4-[3-(1(2)H-Tetrazol-5-yl)propyl]-2-piperidinecarboxylic acid, 'mp' = 257 - 261 (Colombinio Luipli outly of recentionagies S

Analysis calculated for, C₁₀H₁₇N₅O₂ -(1) constant (2) 4-bic Nythet M. H. Theory: C, 50.20; H, 7.16; N, 29.82; Found: C, 49.90; H, 7.23; N, 29.52 in this year of the monoid

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Example 3

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cis-(±)-4-[(1(2)H-Tetrazol-5-yl)methyl]-2-piperidinecarboxylic acid

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To a solution of 30.5 g (0.24 mol) of 4-methoxypyridine-N-oxide in 250 ml of methylene chloride was a added 30.3 g (0.31 mol) 40.7 ml) of trimethylsilyt cyanide. Approximately five minutes later 32.8 g (0.31 mol) 28.0 ml) of N;N-dimethylcarbamoyl chloride was added in four 7 ml portions over one hour. The approximately mixture was stirred overnight at room temperature. To the mixture was carefully added 250 ml of 10% by weight aqueous potassium carbonate. After 15 minutes at room temperature, the organic layer was see separated and the aqueous layer was extracted twice with methylene chloride and once with diethyl ether.

The combined organic extracts were dried over anhydrous magnesium sulfate, (filtered and concentrated under vacuum. The residue was dissolved in 150 ml of 48% by weight aqueous hydrobromic acid. The resulting mixture was heated to reflux overnight and cooled to 0°C. The crystals that formed were collected by vacuum filtration, washed with diethyl either, and dried under exacuum at 50°C to afford 45.5 grof 4-hydroxy-2-pyridinecarboxylic acid hydrobromide.

Ethyl a cyanomangularene-15-horbacycanoch-15-pahendheadachboxytate (9.00 g. 0.031 mol) was hydrogos nated an 4-th set open temperature and 6.5 by subject central with 5.5 by subject central conscious at room temperature, and 5.5 by subject the subject of 6.5 mixture was filtered the biological physical chromatophylip of the restrict provided state of a try size of secure constances. The restrict provided state of a try size of secure constances of the restrict provided state of a try size of secure constances.

To a 1 I. round bottom flask was added 45.5 g (0.21 mol) of 4-hydroxy-2-pyridinecarboxylic acid 25% hydrobromide and 5000ml of ethanol saturated with hydrochloric acid. The mixture was heated to reflux recovery overnights cooled and concentrated under vacuum to 1/3 of its original volume. After cooling the mixture to about 0.5 C; the resultant crystals were collected by vacuum filtration, washed with ethanol and diethyl ether, ்கள்ளை dried under vacuum to afford 29.5 g of ethyl 4-hydroxy-2-pyridinecarboxylate hydrochloride மு vactium and partitioned between 6W seuscoup hydrothlanks acid and diethyl either. The layers were separated and the aqueous layer extracted soain with diethyl ether. The aquious layer was concentration cow Co.Ethyl cis-4-hydroxy-N-t-butoxycarbonyl-2-piperidinecarboxylate allowed each earlier and concerns the control of the con heated to rollow oversight, cooled to room temperature and concentrated under vectors. The residue was ಾರ್ಜಿಯ ವಿ:Ethyl: 4-hydroxy-2-pyridinecarbôxyláte: hydrochloride:(27;2 g,:0.13 mol): was: hydrogenated:in:200,ml of zeo rethanol with 15.5 g of 5% by weight modium on alumina at 100 C and 1000 p.s.ii: for 10 hours. 不he mixture selle was repoled thered and report rated ander vacuum a Toethearesidue twas added ≥250 and of methylene @mirchloride, 150 ml of ethanol and 25;2 g (0.20 mol) 34:0 ml) of Hunig's base ifollowed by the dropwise addition heborofiz28.4 gr(0.13 molig29.9 ml) of distributyldicarbonate over apperiod of thirty minutes hAfter one hour the mixture was concentrated under vacuum, and the residue was dissolved in methylene chloride and washed twice with 10% by weight aqueous sodium bisulfate. The combined aqueous washes were extracted once with methylene chloride and once with diethyl ether. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. High pressure liquid chromatography of the residue provided 21.3 g of ethyl cis-4-hydroxy-N-t-butoxycarbonyl-2-piperidinecarboxylate as a colorless CC. 12 M. 1 C. 46 38 1 D. V. 445 Theory: Found.

D. Ethyl 4-oxo-N-t-butoxycarbonyl-2-piperidinecarboxylate

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To a 1 l. round bottom flask was added 33.6 g (0.16 mol) of pyridinium chlorochromate, 35 g of powdered 4A molecular sleves and 200 ml of methylene chloride. After stirring the mixture at room temperature for sixty minutes, a solution of 21.3 g (0.078 mol) of ethyl cis-4-hydroxy-N-t-butoxycarbonyl-2-piperidinecarboxylate in 50 ml of methylene chloride was added. After stirring the mixture for sixty minutes at room temperature, 700 ml of diethyl ether was added. The mixture was filtered through three-fourths inch of Celite and three-fourths inch of silica gel (230-400 mesh) in a 650 ml medium porosity sintered glass funnel. The solids were washed with 1 l. of diethyl ether and the filtrate was concentrated under vacuum. To the residue was added 200 ml of diethyl ether and the mixture filtered through three-eighths inch of Celite and three-eighths inch of silica gel (230-400 mesh) in a 150 ml medium porosity sintered glass funnel. The solids were washed with 500 ml of diethyl ether and the filtrate was concentrated under vacuum. The residue was purified by high pressure liquid chromatography to provide 14.6 g of ethyl 4-oxo-N-t-

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butoxycarbonyl-2-piperidinecarboxylate as a colorless oil.

E. Ethyl 4-cyanomethylidene-N-t-butoxycarbonyl-2-piperidinecarboxylate.

To a suspension of 0.75 g (0.019 mol, 60% by weight in oil) of sodium hydride (washed three times with hexanes) in 40 ml of THF was added 3.34 g (0.019 mol) of diethylcyanomethylphosphonate. After stirring the reaction mixture for thirty minutes at room temperature, a solution of 4.26 g (0.016 mol) of ethyl 4-oxo-N-t-butoxycarbonyl-2-piperidinecarboxylate in 10 ml of THE was added: The mixture was stirred for 30 minutes at room temperature and 90 minutes at the reflux temperature of the reaction mixture, then cooled to room temperature and quenched with water. The organic layer was separated and the aqueous layer extracted twice with idiethyl ether. The organic extracts, were acombined adried lover canhydrous amilianginesium sulfate, filtered and concentrated under vacuum. High pressure liquid chromatography of the residue afforded 3.58 g of ethyl 4-cyanomethylidene-N-t-butoxycarbonyl-2-piperidinecarboxylatego and ands, vacuum. The neutrino was diseased in 190 to 190 to 190 to 190 diseased by the property and

percence one a region that their superiors of the court, firm traphiese where of percent and ending prilinger ** F. Ethyl cis-4-cyanomethyl-N-t-butoxycarbonyl-2-piperidinecarboxylate.

Ethyl 4-cyanomethylidene-N-t-butoxycarbonyl-2-piperidinecarboxylate (9.00 g, 0.031 mol) was hydrogenated in 140 ml of ethanol with 0.90 g of 5% by weight palladium-on-carbon at room temperature and 60 p.s.i. for 60 minutes. The mixture was filtered through Celite and concentrated under vacuum. High pressure liquid chromatography of the residue provided 8.20 g of ethyl cis-4-cyanomethyl-N-t-butoxycarbonyl-2-

plos piperidinecarboxylatexxicuy(see to floor (ELG) (; ELGA patible (www. Hash) motion become in a late a late யின் இ இEthyl‡cis-4-cyanomethyl-N-t-butoxycarbonyl-2-piperidinecarboxylate (8.0ஐர. 27,0 mmol)എand 47.9ஐ 25 7 (54:0 (mmol)) tributyltin (azide) were heated, to 80 (Cafony72-bhours a The mixture, was a cooled a to groom ्रिक्टी temperature and charged with 10 ml:of methanol. To this solution was added 100 ml:of methanol saturated with hydrochloric gas. After stirring for two hours at room temperature; the mixture was concentrated under vacuum and partitioned between 6N aqueous hydrochloric acid and diethyl ether. The layers were separated and the aqueous layer extracted again with diethyl ether. The aqueous layer was concentrated under vacuum. The residue was dissolved in 70 mt of 6N aqueous hydrochloric; acid. The mixture was heated to reflux overnight, cooled to room temperature and concentrated under vacuum. The residue was to imdissolved in water) treated (with 6 mil. of propylene oxide at 50 octors one hour, and concentrated under ையில் residue was ladded 75 ml of ethanol and the resulting mixture was heated at reflux for one eneithour. The mixture was cooled, and the resultant precipitate was collected by vacuum filtration, and washed 35 with ethanol and acetone. The precipitate was suspended in acetone and refluxed for one hour. The mixture

was cooled and filtered. The precipitate was washed with racetone and diethyl, ether, and dried ander berevactume to afford: 3.0; groficis-(±)-4-[(1(2)H-tetrazol-5-yl)methyl]-2-piperidinecarboxylic; acid; acetone, solvate. notice with 10% by yieldn't action screen bisulates. This companies in the property of the screen with the boundary screen action of the screen with the screen action of the scr

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Theory: C, 46.68; H, 7.44; N, 27.22; C, 46.58; N, 27.28. Found: H, 7.12;

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Z-(±)-4-[(1(2)H-Tetrazol-5-yl)methylidene]-2-piperidinecarboxylic acid

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2/ 3. A 2.16 g portion of ethyl 4-cyanomethylidene N-methoxycarbonyl-2-piperidinecarboxylate (prepared according to steps A-E of Example 3 above) was dissolved in 5 ml of dimethyl ether, and 5.69 g of tributyltin azide was added. The mixture was stirred at 80 °C for six days. A total of 6 g of additional azide was added from time to time during the reaction. The mixture was cooled at the end of the reaction period, and 50 ml of diethyl ether was added. Hydrogen chloride gas was bubbled through the solution for about five minutes, until it became cloudy, and the mixture was then concentrated under vacuum. Fifty ml of

acetonitrile was added, and the mixture was extracted five times with a total of 500 ml of hexane. The hexane extracts were discarded, and the acetonitrile layer was concentrated under vacuum. The residue was chromatographed on 100 g of silica gel, eluting with 4% acetic acid in diethyl ether. The productcontaining fractions were combined and concentrated under vacuum to obtain 1.7 g of crude product, which was heated under reflux with 70 ml of 6N hydrochloric acid for 20 hours. The mixture was then cooled and concentrated under vacuum to obtain a solid product. Water was added, and the solid was filtered and washed with acetone and ether and dried under vacuum to afford 0.42 g of product as the dihydrate.

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	Analysis calculated for C ₈ H ₁₁ N ₅ O ₂ 2H ₂ O and to beinth as wire yet omages	
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Butyl cis-(±)-4-[(1(2)H-tetrazol-5-yl)methyl]-2-piperidinecarboxylate

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A 1.02 g portion of the product of Example 3 was esterified by adding it to 250 ml of n-butanol, saturated with hydrogen chloride. The mixture was heated under reflux overnight, and was then cooled and concentrated under vacuum. The residue was dissolved in water, and was purified by eluting it through an ion exchange column with 10% pyridine in water. The product-containing fractions were combined and concentrated under vacuum, and the residue was suspended in acetone and heated under reflux for one hour. That mixture was then filtered, and the filtrate was concentrated under vacuum. The residue was taken up in diethyl ether, and that mixture was filtered. The solids were washed with diethyl ether, to obtain 0.50 g

of the desired product mp = 182 -185 C. The same evaluation of the desired product mp = 185 c. The same the same of the desired product me to the same the same that the same of the same the invention which is eac<u>ieles of birelden one are independented</u> in the ecopens. The particular doca reliabling and ye bandowler ar Transian Analysis calculated for C12H21N5O2 on the retaining a brungmon to the route of administration, the circumstances surroundin N. 26.20; C, 53.92; H, 7.92; Theory: a ye besides once of her three particular condition beind N, 26.05 Found: C, 53.66; H. 8.02: 35 FALICAUMESTIN LEGGREVITTEN variety of routes include

threasel routes: A typical delay does the some in the Committee of the against A typical delay in the active **compound of this** invention. Prereved daily doese with parameter 20% to signer of mighty, ideally about 0.1 to

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A 1.05 g portion of the product of Example 3 was esterified in ethanol, sustantially as described in Example 5 above, except that the solid obtained after ion exchange was unsoluble in acetone and so it was enfiltered, washing with acetone and diethyl ether to obtain 0.75 g of the desired product, mp = 98 to 101 °C.

Analysis o	calculated for	C10H17N5C	Male Charles Timor C 0.95H ₂ O 0.95H ₂ O or cade to be careful to the cade to
Theory:	C, 46.84;	H, 7.43;	N, 27.3]\$66 v. c) tohn telev. one beel N, 27.91cc qui existente Ezelet.
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Four g of ethyl cis-(±)-4-[(1(2)H-tetrazol-5-yl)methyl]-N-methoxycarbonyl-2-piperidinecarboxylate was added to 0.6 g of sodium hydride in 16 ml of dimethyl formamide. The solution was stirred under nitrogen for one hour, and then 1.9 g of methyl iodide was added in 1 ml of dimethyl formamide. The mixture was stirred overnight at ambient temperature, and then 0.06 g of additional hydride was added and the mixture was stirred for three hours more. About 2 ml of water was added slowly to quench the hydride, and then the mixture was concentrated under vacuum. The residue was taken up with ethyl acetate and water, and the organic layer was dried over magnesium sulfate and concentrated under vacuum to obtain 3.2 g of residue. The crude product was purified by chromatography over 250 g of silica gel, eluting with 7:3 isopropanol:acetic acid. The product-containing fractions were concentrated under vacuum to obtain 1.47 g of product, in the blocked form.

A 1.39 g portion of the above intermediate was added to 50 ml of 6N hydrochloric acid, and the mixture was heated under reflux overnight and cooled. It was then concentrated under vacuum, and the residue was purified on an ion exchange column, eluting with 10% pyridine in water. The product-containing fractions were combined and concentrated under vacuum, and the residue was heated under reflux in acetone for one hour. The mixture was then cooled and filtered, and the residue was oven-dried to obtain 0.184 g of the desired product, in hydrate form.

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Theory: (C, 43.47; dHy/Z:13; is)N,:28.16; if to nechoo ; £0,) A	บยิ
Found: C, 43.78; 6H, 6.71; r N, 27.82, dr p regarded from between	

As noted above, the compounds of this invention are excitatory amino acid antagonists. Therefore, another embodiment of the present invention is a method of blocking one or more excitatory amino acid preceptors in mammals which comprises administering to a mammal requiring decreased excitatory amino acid neurotransmission a pharmaceutically effective amount of a compound of the invention.

The term "pharmaceutically effective amount", as used herein, represents an amount of a compound of the invention which is capable of blocking one or more excitatory amino acid receptors. The particular dose of compound administered according to this invention will, of course be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes. A typical daily dose will contain from about 0.01 mg/kg to about 20 mg/kg of the active compound of this invention. Preferred daily doses will be about 0.05 to about 10 mg/kg, ideally about 0.1 to about 5 mg/kg.

A variety of physiologic functions have been shown to be subject to influence by excessive stimulation of excitatory amino acid neurotransmission. As such, the compounds of the present invention are believed to have the ability to treat a variety of disorders in mammals associated with this condition which include neurological disorders such as convulsive disorders for example, epilepsy; stroke; anxiety; cerebral ischaemia; muscular spasms; and neurodegenerative disorders such as Alzheimer's Disease and Huntington's Disease. Therefore, the present invention also provides methods of treating the above disorders at

The following experiment was conducted to demonstrate the ability of the compounds of the present invention to inhibit responses due to excitatory amino acid agonists. A typical receptor substance is characterized by N-methyl-D-aspartic acid (NMDA).

Male Charles River CF1 mice held in the laboratory for a minimum of three days were housed, 12 per cage, on sawdust bedding in clear plastic boxes with wire mesh lids. Animals were allowed full access to feed and water prior to testing.

Unless otherwise specified, all test compounds were formulated in dimethylsulfoxide (DMSO) and diluted to a 5% DMSO/sterile water solution by volume. Dosing began at 160 mg/kg. If any significant activity was detected, the test drug dose was divided in half until no more activity was detected. All test compounds were administered using the intraperitoneal injection (i.p.) route at a volume of 0.01 cc/gm.

Five mice were taken from the plastic cages, dosed with the test compound and placed individually in clear plastic observation cages. After a 30 minute drug absorption period, the mice were injected intraperitoneally with 200 mg/kg of NMDA. This dose of NMDA produces death in more than 95% of control-treated animals. Twenty minutes after the NMDA injection the animals were scored as dead or alive. Data

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are reported as the minimum effective dose (MED) to block NMDA-induced lethality. Protection from entilethality issued by the survival of satisfact three of the fliver animals. The data is set forth, in Table 1, below. Data for AP5 and AP7, known excitatory, amino acid antagonists, are provided for comparison at beingel.

The following formulation examples are illustrative only and are not intended to limit its scope of the invention in any way.

		In Vivo NMDA Induced			
	198	Example No. of Compound Tested	MED (mg/kg)	rd gelatin capquies are are	r.) i
Guarnity (mg/onosula)	T SOUTH WORLD DELLE	2	20 10 10		
, 250 200 10 460 mg	tic sold		160 160 160 80 160	(+)-4-(3-(1/2)H-Telhaz: clarch, dired mògredium smarate Total	

In another experiment, male or female neonatal (7 to 8 days old) Sprague-Dawley rats were removed from the dam and placed in plastic observation that were maintained at 30-32 °C. All test drugs were dissolved in normal saline. Activation of NMDA receptors in these rats leads to a readily observable generalized motor seizure in over 95% of the animals. These seizures are not blocked by administration of a non-NMDA selective antagonist drug, but are readily blocked by NMDA selective compounds.

Animals were injected by the intraperitoneal route with the test drug (1 ml/100 g of body weight) and observed for a 30 minute period for seizure (potential agonist) activity. They were then injected with NMDA at a dose of 20 mg/kg body weight i.p. to test for antagonist activity. Rats were observed for seizures for an additional 30 minutes following NMDA administration. Animals were rated as being positive or negative for the clear demonstration of tonic-clonic seizure activity with loss of righting ability. Generally, five animals were used at each dose of compound. Doses were decreased in a stepwise fashion-until at least 3 out of 5 animals exhibited seizures. The minimum effective dose was the lowest test dose which prevented NMDA-induced seizures in at least three out of five animals.

The MED of Example 6 in the above test was 200 mg/kg.

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The compounds of the present invention are preferably formulated prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical formulation comprising a compound of the invention and a pharmaceutically acceptable carrier, diluent or excipient therefor.

The present pharmaceutical formulations are prepared by iknown procedures using well known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol. (as a solid corpinal liquid medium), continents containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, lalginates, tragacanth gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl-and propyl-hydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing

55 procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg, more usually about 25 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other

most, noncered a visitable, populative and a second publishes and a second parameters maintain and as beinger and workmammals, leach unit containing a predetermined quantity of sactive/material, calculated no approduce; the desired therapeutic effect, in association with a suitable pharmaceutical carrier in 174A bits CRA vol ats0.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

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Hard gelatin capsules are prepared using the following ingredients:

	0°	8 1	Quantity (mg/capsule)
(+)-4-[3-(1(2)H-Tetraz starch, dried magnesium stearate Total	zol-5-yl)propyl]-2-p	iperidinecarboxylic acid	250 200 <u>10</u> 460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities. from the dam and placed in pleatic observation characters that were injurialised at 30 dz C. Ab rest dings were discoved in normal antine. Activation of NMDA receptors in these rats leads to a resulty observable to notativinimbs yet beyond for one requires an Eormulation. 2 on to 2000 the control of the con a non-MACDA selective antagonist drug, but are readily blocked by NWDA selective compounds. Animals considered by the interpertupous control of the property of the proper elements of the common points of common specific of the common of the co additional (i) retinancial wing Milita administration. Aministration as being positive or negative for the clear dis(teldat/gm) of tonic-closed season activity; his ties of righting shifty. Gene ally, five animate at least 3 out of 5 o secu 250 in been every -ACIMM pernever (+)-4-[(1(2)H-Tetrazol-5-yl)methyl]-2-piperidinecarboxylic acid sel is migrus ne paorbni cellulose, microcrystalline The Mile C Example silicon dioxide, fumed Fin the above sest was 200 mg/kg. stearic acid by benefit of the second of the **วราตา**อาธาร : กอยสา 665 mg and a chambosufficiely acceptable curves, district to acceptent the efor

The present ign 266 innighted and compressed to formitablest each engine in the present in the present and a composition of the present in the present in the score ingredient will be mixed with a company of dictional by a correct or situation as a circle of the present of the

Joildhor Leagues (Scotter) Section (Scotter) (

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30 °C. and transferred to a filling device. The required amount is then field to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

CARGA COLORD

7 451010	ach containing 60 mg of active ingredient are made as follows:	muiz ae	
	(±)-3-[2-(1(2)H-Tetrazol-5-yl)ethyl]-2-piperidinecarboxylic acid	60 mg	
:	starch	45.mg	
, '1	microcrystalline cellulose	35 mg	
· · · · · · · · · · · · · · · · · · ·	polyvinylpyrrolidone (as 10% solution in water) hard on setting	osa 4.mg	
,	sodium carboxymethyl starch	4.5-mg	
	magnesium stearate talc talc consistence in the consistence of the consistence in the consistence of the	0.5 mg	am erlî
dulic eys roloc i	VIEW STREET A WINDOW SERVICE STREET, ASSESS STREET,	150 mg	ymethyl cal
MUDBY OF SOUR	of the contract of the contrac	and the second of the	l emics ritiw

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a

20 tablet machine to yield tablets each weighing 150 mg. berageigt ad your natural to represent in A

Formulation 5 enliss circulation and the constant of the circulation o

s of otor Capsules each containing 80 mg of medicament are made as follows: woos will be actuales enti-

subject in resul of treatment.

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(±)-3-[3-(1(2)H-Tetrazol-5-yl)propyl]-2-piperidinecarboxylic acid	80 mg	
starch	59 mg	
microcrystalline cellulose	59 mg	Claims
magnesium stearate	2 mg	20.4
magnesium stearate siumot en	"200 mg"	30 P

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories each containing 225 mg of active ingredient may be made as follows:

(±)-4-[2-(1(2)H-Tetrazol-5-yl)ethyl]-2-piperidinecarboxylic acid	225 mg
saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions each containing 50 mg of medicament per 5 ml dose are made as follows:

(±)-4-[2-(1(2)H-Tetrazol-5-yl)ethyl]-2-pi sodium carboxymethyl cellulose	iperidinecarboxylic acid	50 mg	elaldsT
syrup benzoic acid solution	in deliv Chairmer 443)	1.25 ml 20:10 ml	
flavor color purified water to total	strijne reduics Symolyche (as felic o d	n ruorai q.v.	

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required

bed in the every the content of the

An intravenous formulation may be prepared as follows: "Higher done stocked block of coliform felder". 95

(±)-4-[2-(1(2)H-Tetrazol-5-yl)ethyl]-2-piperidinecarboxylic acid isotonic saline

The solution of the above ingredients is administered intravenously at a rate of 4 ml per minute to a subject in need of treatment.

Day 95 Dips of years an analogic fly and years are TH(\$\text{S}\text{T}\text{S}\text{F}\text{C}(2)

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wherein:

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H2 is hydrogen or C1-C3 alkyl;

n is 0, 1, 2 or 3;

m is 0 or 1;

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provided that the sum of m and n is 0, 1, 2 or 3;

R3 is hydrogen, C1-C4 alkyl, phenyl or an oral ester forming group;

a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein R1 is

C) alloyating a compound of the formula

- C OR3.

3. A compound of Claim 1 or 2 wherein R² and R³ are hydrogen.

4. cis-(±)-4-[(1(2)H-Tetrazol-5-yl)methyl]-2-piperidinecarboxylic acid or a pharmaceutically acceptable

5. cis-(±)-4-[2-(1(2)H-Tetrazol-5-yl)ethyl]-2-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof.

6. cis-(±)-4-[3-(1(2)H-Tetrazol-5-yl)propyl]-2-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof.

7. Z-(±)-4-[(1(2)H-Tetrazol-5-yi)methylidene]-2-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof.

8. A compound of any one of the preceding claims for use in blocking one or more excitatory amino acid receptors in mammals.

9. A pharmaceutical formulation comprising as an active agent a compound of any one of Claims 1 to 7 associated with one or more pharmaceutically acceptable carriers or diluents therefor.

10. A process for preparing a compound of any one of Claims 1 to 7 comprising:

A) esterifying a compound of the formula

with an alcohol of the formula HOR3, wherein R3 is C1-C4 alkyl, phenyl or an oral ester forming group; B) aminating a compound of the formula

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with an amine of the formula HN(R⁴)₂, HNHSO₂R³ or HNHCO₃R³ and the eldestococcable accordance in the formula of the formula.

20 C) alkylating a compound of the formula at 153 Alexander 1 miels to brivagings A.S.

G. DRP. 3. A coincount of Citim 1 of 2 yeleswin R^c and R^c are hydrogen

4. cls-(s)-4-((1(2))-7-otrazot-5-yl)methylj-2-pipulidineca.bollilic acid or a pharmaceutinarly acceptable asit thereof.

N N Statement of the second of the

5. da-(z)-4-(2)-12/PP-Tetrazoi-8-yf)-sitryli-2-pipericina erboxylio acid or a phermureulically acceptable self-sherrori.

5. de-(1) 4 (5-(1/2)/4-Tetrazal-6-y/pp.payl)-2-piperi(cH2)) poxylic acid or a pharmecautically acceptable estil trereof.

7. Z-(1)-4(1)(2)/4-Tetrazal-5-yl)methylidenej-2-piperidinuca@divilic cold or a pharmacautically acceptable.

able celt tricked.

8. A compound of any one of the preceding claims for use in blocking one or more excitatory amino acid receptors in naminate.

3. A pharmaceutical formulation comprising as an ichine seed a more of charmaceutically acceptable carrier of diffused at therefore.

10. A process for prepenting a compound of any one of Stalms 1 to 7 periorising.

A) estantising a compound of the ionaula.

with a halide of the formula X-R² wherein R² is C₁-C₃ alkyl and X is bromo, chloro or iodo;

D) deblocking a compound of the formula

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by acidic or basic hydrolysis; or

E) preparing a salt of a compound of formula I with an acidic or basic salt-forming reagent.

Claims for the following Contracting States: GR; ES

1. A process for preparing a compound of the formula

(CH₂)_n

 $\bar{\lambda}$ \bar{L}

with an abonoi of the formula MORS, wherein RS is Gy Ca. siMI. You'd or an area user forming group.

8) arritating a compound of the formula

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N R1

wherein:

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11(2) 13

N-R²

With an ainine of the formula HM(R²);; HMHSO₂H² or HNHCO

O) alkyleting a compound of the formula

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R² is hydrogen or C₁-C₃ alkyl;

n is 0, 1, 2 or 3;

m is 0 or 1;

provided that the sum of m and n is 0, 1, 2 or 3;

R³ is hydrogen, C1-C4 alkyl, phenyl or an oral ester forming group;

each R⁴ is independently hydrogen, C₁-C₄ alkyl or phenyl; or a pharmaceutically acceptable salt thereof; comprising:

A) esterifying a compound of the formula

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with an alcohol of the formula HOR3, wherein R3 is C1-C4 alkyl, phenyl or an oral ester forming group; B) aminating a compound of the formula

wherein:

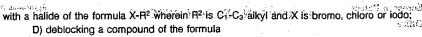
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with an amine of the formula HN(R4)2, HNHSO2R3 or HNHCOR3; C) alkylating a compound of the formula

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2. A process of Claim, fafor preparing a compound of formula I wherein R!! is -COOR3; wherein/R3 is C1-C4 alkyl, phenyl or an oral ester forming group, comprising esterifying a compound of formula II with an alcohol of the formula HOR3 in the presence of a coupling agent or hydrogen chloride gas and a mutual Obio, US; 6.6.5, COLLINS et al.: "Some organic solvent.

A process of Claim 1 for preparing a compound of formula I wherein R1 is COOR3 wherein R3 is -CON(R1)2, -CONHSOOR3, or -CONHCOR3, comprising aminating a compound of formula: It with an amine of the formula HN(R4)2, HNHSOOR3, or HNHCOR35 in the presence of a coupling agent and a mutual organic solvent. cortex slice"; & BRAIN RES. 1982,

1 tor preparing a compound of formula I wherein (R2 is C1-Catalkyl comprising alkylating a compound of formula III with a halide of the formula X-R2 in the presence of a strong base and a mutual organic solvent.

5. A process of Claim 1 for preparing a compound of formula I wherein R1 is -COOH comprising deblocking a compound of formula IV by acidic or basic hydrolysis at from about 50 °C. to about 150 °C.

6. A process of Claim 1 for preparing a pharmaceutically acceptable salt of formula I comprising reacting a compound of formula I with an acidic or basic salt-forming reagent in solution in an organic or aqueous solvent.

7. A process for preparing a pharmaceutical formulation comprising admixing a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined in any one of Claims 1 to 6 with one or more

pharmaceutically acceptable carriers or diluents therefor. MASS C V F र प्रकार - महिल्लीको स्वर्वेश्यो प्रकार केले किर स्वर्वाकर के जिल्हा के उर्जाव है के व्यवस्था के वर्ष का की अधि होता है कहा जब अधि अधि के व्यवस्था है कि अधि के व्यवस्था स्थानक विकास स्थापन Theory when the factor to the



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